Impact of the Orphan Drug Tax Credit on treatments for rare diseases

Prepared for the Biotechnology Industry Organization and the National Organization for Rare Disorders

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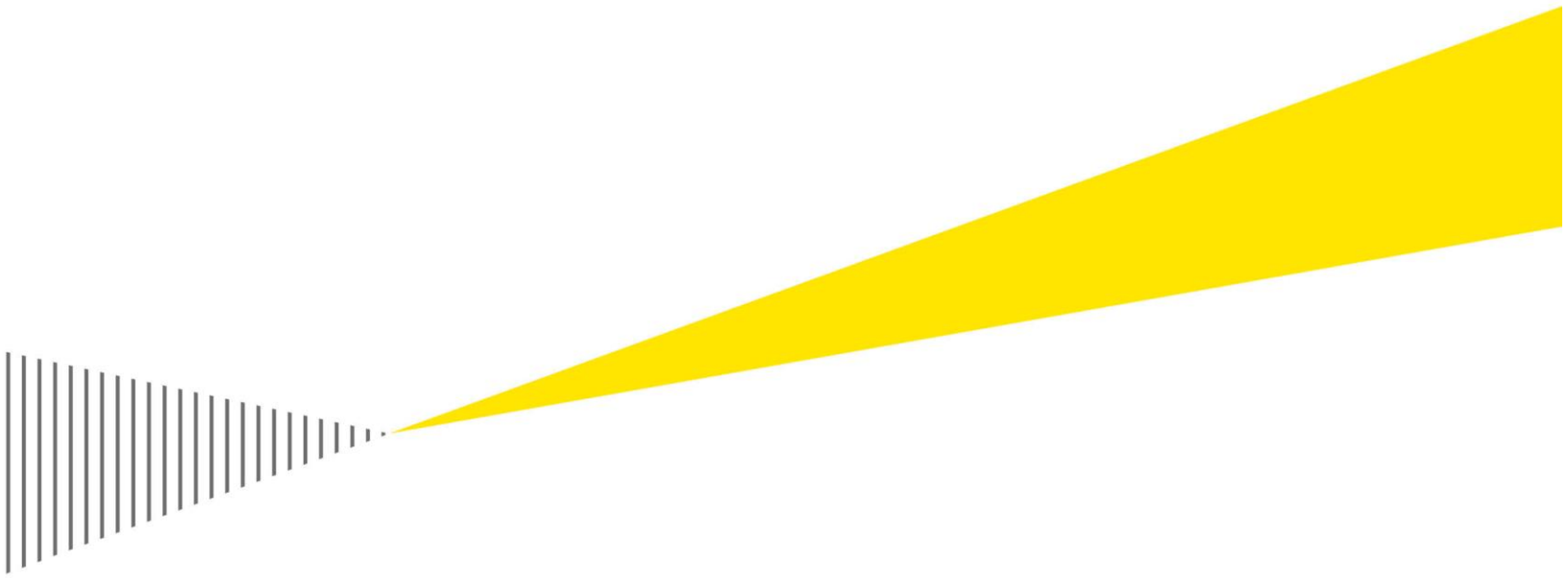

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Executive summary

Nearly 30 million Americans suffer from a rare disease or condition. Despite the large number of patients living with rare diseases, only four percent of rare diseases have an approved treatment. As such, many patients suffering from a rare disease lack any treatment options.

Before the Orphan Drug Act (ODA) was enacted in 1983, drug developers were often hesitant to invest in developing new treatments for rare diseases because the small patient populations made it difficult to recover development costs. For rare diseases, clinical trial costs alone can total thousands of dollars per person diagnosed with the disease. Promising new drugs to treat rare diseases could languish without a sponsor willing to fund further development – hence the term "orphan drug."

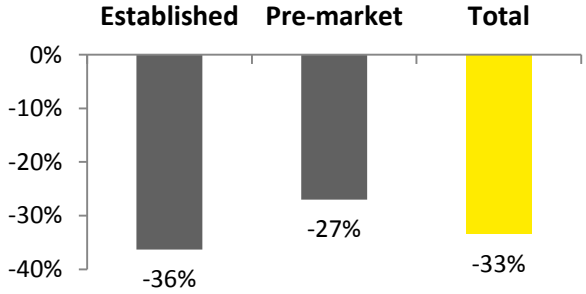
Rising investment in treatments for rare diseases can be attributed in large part to the incentives provided by the ODA. Since the law's enactment, 486 orphan products have been approved, which includes a mix of more effective formulations, new indications, dosages, and sources of supply. In that time, more than 200 new orphan drugs have been approved by the Food and Drug Administration (FDA) – compared with only 34 approved before enactment of the ODA. This report defines new orphan drugs as new molecular entities (NMEs) and new biologic license applications (BLAs) that have been approved by the Food and Drug Administration (FDA).

One of the ODA's key provisions is the Orphan Drug Tax Credit (ODTC), which is designed to promote research spending on orphan drug development. The ODTC allows orphan drug developers to receive a tax credit for 50 percent of qualified clinical trial costs for new orphan drugs. By lowering development costs, the ODTC makes it more likely that treatments for rare diseases will advance from the lab and be developed. More general R&D incentives may also provide important societal benefits but may generally encourage investment to flow into research activities that carry less risk and offer more reward than treatments for rare diseases.

This report uses detailed data on the costs and timeline of drug development to construct an economic model of the impact of the ODTC on the cost of, and investment in, orphan drug development. This type of cost of capital framework is a methodology commonly used to analyze the impacts of changes in tax policy on investment incentives. This report's key findings are:

- Without the ODTC, it is estimated that investment in orphan drugs would have been smaller by a third both historically and in the future (Figure ES-1).
- In the absence of the ODTC, 67 orphan drugs, or 33%, would likely not have been developed over the past 30 years.

Figure ES-1: Estimated decline in investment in orphan drugs by type of developer under potential ODTC repeal



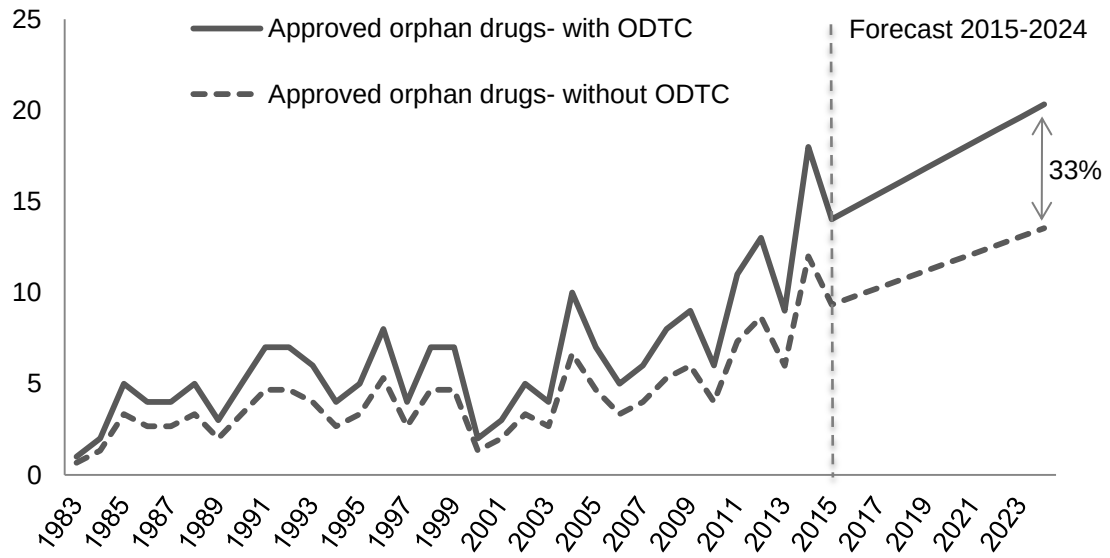
Source: EY analysis.

► Going forward, if the ODTC were repealed, it is estimated that 57, or 33%, fewer new orphan drugs would be approved over the next 10 years.

As shown in Figure ES-1, pre-market companies without existing drug portfolios would see a smaller decline because they cannot use tax credits until they begin to have tax liability, often not until after their first drug is approved. This is not to imply that the ODTC is not valuable for pre-market companies. In the absence of the ODTC, the net cost to a pre-market company of developing an orphan drug would increase by 30 percent. Despite the reduced incentives offered to pre-market companies, smaller companies are heavy users of the benefits offered by the ODA. Nearly a third of all companies receiving an orphan drug approval had never had a drug approved before.

Figure ES-2 shows the number of new orphan drugs that received FDA approval between 1983 and 2014. In 2014, the FDA approved more new drugs – orphan or otherwise – than any time during the previous decade. Figure ES-2 also shows likely future orphan drug approvals – based on historical growth rates – from 2015 to 2024. The dashed line in the figure shows an estimate of the number of approved orphan drugs if the ODTC had not been enacted. From 1983 through 2014, it is estimated that 67 fewer approved orphan drugs would have been on the market without the ODTC. Based on historical growth rates, if the ODTC were repealed, it is estimated that 57 fewer new orphan drugs would be approved over the next 10 years.

Figure ES-2. Estimated impact of potential ODTC repeal on new orphan drugs



Note: Projection beyond 2014 is based on the annual average change in orphan drug NME and new BLA approvals from 2004 to 2014 with and without the ODTC.
Source: Drug Approval Reports, Food and Drug Administration, various years; EY analysis.

If the ODTC were repealed, the resulting reduction in the number of approved new orphan drugs could have a significant impact on Americans with rare diseases. Only 289 (four percent) of the more than 7,000 identified rare diseases have at least one approved treatment option. Because so few rare diseases have an available treatment, the benefit of new orphan drugs is potentially large. By offering these Americans treatment where

previously none existed, new orphan drugs can affect multiple dimensions of public health including longevity, participation in everyday activities, mobility, and the ability to work. While these benefits can be difficult to measure, they are an important part of the benefit new orphan drugs provide. Patients can benefit from new orphan drugs through longer life spans and higher quality of life, while society as a whole can benefit from increased patient productivity and a potential decline in the amount of resources devoted to health care and related government spending.

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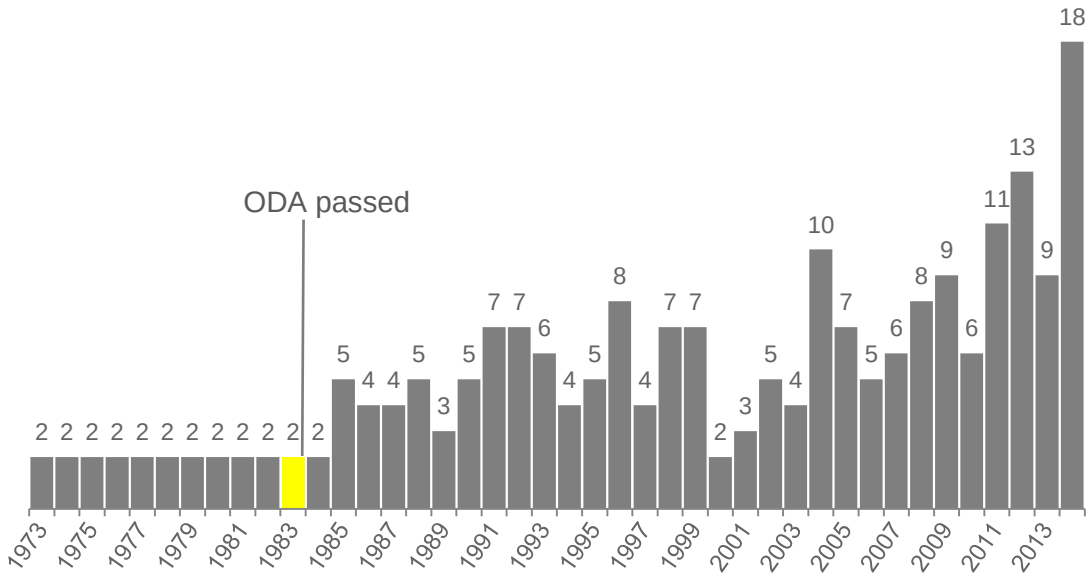
Impact of the Orphan Drug Tax Credit on treatments for rare diseases

1. Introduction

In the United States, nearly one out of every 10 people suffers from a rare disease.[1] Rare diseases are much less likely to have an approved treatment than are more common diseases (see Appendix A for a list of all rare diseases with at least one Food and Drug Administration (FDA) approved treatment). For drugs designed to treat patients with rare diseases, a number of market and regulatory barriers discourage the investment required to find new, potentially life-saving treatments. The Orphan Drug Act (ODA), passed in 1983, was designed to reduce these barriers and spur innovation in the development of new treatments for these patients.

The ODA defines a rare disease as one that affects fewer than 200,000 patients in the United States, and an orphan drug is any drug intended to treat a rare disease. Prior to the ODA, drug developers were often hesitant to invest in developing new treatments for diseases with small patient populations because these treatments offered limited potential to recover development costs. Promising new drugs to treat rare diseases could languish without a sponsor willing to fund further development – hence the term "orphan drug."[2]

Figure 1. New orphan drugs before and after the ODA



Note: New orphan drugs are defined as NMEs or BLAs. Prior to the ODA, the graph shows the average annual number of approved drugs that would have been considered orphan drugs.
Source: Drug Approval Reports, Food and Drug Administration, various years; EY analysis.

When the ODA was passed, it was intended to increase the number of orphan drugs on the market by reducing market and regulatory barriers to the development of new orphan drugs. In the years since the ODA, the number of new orphan drugs has increased dramatically. In this report, new orphan drugs are defined as new molecular entities (NMEs) and new

biologic license applications (BLAs) that the FDA has approved. Figure 1 shows the number of orphan drugs approved each year before and after the ODA was enacted.

Since the ODA, over 200 new orphan drugs have been made available to treat patients suffering from rare diseases. The ODA has increased the number of new orphan drugs by providing drug developers with assistance during multiple stages of drug development. Grants, fee waivers, and tax credits are all ways in which the ODA provides incentives for orphan drug development.

1.1. History of orphan drugs in the United States

By the time the ODA was introduced in December 1981, Congress was increasingly concerned by the lack of orphan drug development.[3] Growing public awareness led to a series of Congressional hearings in the early 1980s that focused on the barriers hindering orphan drug development. At the time, the lack of new orphan drugs was widely attributed to the high cost of drug development and the limited market for treatments of rare diseases.[4]

Congress intended the ODA to help drug developers overcome these barriers and encourage innovation in the treatment of rare diseases.[5] Over time Congress has amended the ODA to further combat barriers to orphan drug development. For example, in 1992, the ODA was amended to include FDA user fee waivers for orphan drug developers, and in 1997, the Orphan Drug Tax Credit (ODTC) was permanently extended.[6] Appendix B highlights some of the key Congressional and other activities related to orphan drugs in the United States.

Since the ODA, other initiatives have promoted additional progress in the treatment of rare diseases. In 2002, legislation created what is today called the Office of Rare Disease Research within the National Institutes of Health (NIH) to coordinate research on treatments for rare diseases. As part of the FDA, the Office of Orphan Products Development (OOPD) oversees the provisions contained in the ODA and administers the Orphan Products Grant Program, which awards approximately $14 million each fiscal year in research grants aimed at supporting orphan drug research.[7] Today, many different networks and organizations, such as the National Organization for Rare Disorders (NORD), help facilitate research and patient support in the United States and other countries.

2. Barriers to orphan drug development before the ODA

Prior to enactment of the ODA in 1983, very few orphan drugs were available on the market to treat patients with rare diseases. It is estimated that only 34 orphan drugs were approved before the ODA.[8] There have been over 200 approved since. A combination of market and regulatory barriers limited the ability of drug developers to bring new orphan drugs to market, and, while many of those barriers remain in place today, the ODA has significantly reduced their impact.

2.1. Market barriers

The two most significant market barriers to the development of new orphan drugs are high development costs and limited patient populations. Each new orphan drug requires a substantial investment in research and development with limited chance the drug will make it to market. The small pool of potential patients further reduces a drug developer's ability to recover their research investment.

Drug development costs are high in part because relatively few drugs make it through the development process. By the time compounds enter the preclinical phase of testing, only 1 out of 5 remaining drugs will receive market approval.[9] The total research and development cost to produce a single approved drug includes not only the cost to develop the successful approved drug, but also the cost of the unsuccessful drugs.

Before the ODA came into effect, academic research began to show rising drug development costs.[10] In the 1970s, the total cost of bringing a new drug to market was $182 million (in 2014 dollars), and by the 1980s, that number had risen to $205 million (in 2014 dollars).[11] A 2007 estimate of the total cost to bring a new drug to market is $1.5 billion (in 2014 dollars).[12] A not-yet-released study indicates that costs have risen to $2.6 billion (in 2014 dollars).[13] The total cost of bringing a new drug to market includes: out-of-pocket costs, the cost of failures (since most new compounds are never approved), and the cost of capital.

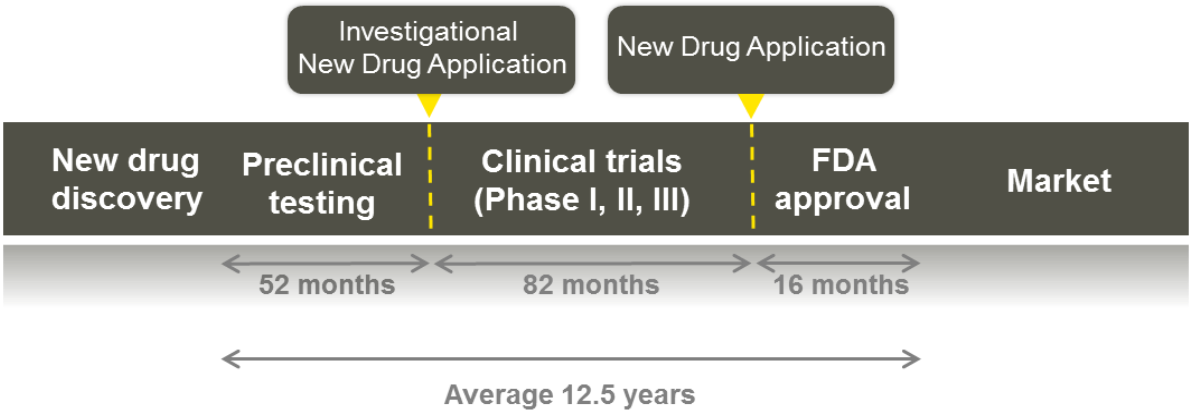
After a drug receives market approval, the developer can begin to recover its investment in the discovery and research process. For orphan drugs, the opportunity is diminished due to the limited pool of potential patients, which is one reason many drug developers find it difficult to justify the investment required to develop treatments for rare diseases. According to the ODA, orphan drugs are designed to treat conditions that exist in less than 200,000 patients in the United States, and for many rare diseases, the number of cases may be far less than 200,000.[14]

Spreading the cost of developing a new drug over small patient populations could result in a per-patient cost of tens of thousands of dollars. As a result, prior to the ODA, many promising discoveries never received the investments required to turn them into viable orphan drugs.

2.2. Regulatory barriers

In addition to high costs and other market-based disincentives, significant regulatory barriers existed prior to the ODA. A robust and comprehensive FDA approval process is important to ensure drugs reaching the market are safe and efficacious, but it also increases the timeline and cost of drug development. As shown in Figure 2, it takes an average of 12.5 years and $1.5 billion (in 2014 dollars) to bring a new drug from the preclinical stage through FDA market approval.[15] For potential developers of new orphan drugs, who have a limited patient pool from which to recover these costs, the incentives available under the ODA can be a factor in determining which investments to pursue.

Figure 2. Typical drug development timeline



Source: Joseph A. DiMasi and Henry G. Grabowski, "The cost of biopharmaceutical R&D: is biotech different?" *Managerial and Decision Economics,* (John Wiley & Sons, Ltd, 2007).

Once a new potential drug is discovered it enters preclinical testing during which initial safety assessments take place in a laboratory. Before being tested in humans (i.e., clinical trials), the developer must submit an Investigational New Drug Application (IND) to the FDA. Once the FDA approves the IND, clinical trials can begin.

Clinical testing culminates in Phase III with randomized trials in human volunteers. This phase can be particularly challenging for developers of orphan drugs who may struggle to find the necessary number of trial participants to achieve statistically significant results.

If a drug successfully completes each clinical trial phase, the developer can submit a New Drug Application (NDA) or Biologic License Application (BLA) to the FDA for market approval. If the FDA grants market approval, the treatment becomes available to patients. Once a drug becomes available to patients, the costs of development may not end. Though not included in Figure 2, the FDA can require drug developers to participate in Phase IV post-market monitoring, which may further increase the overall costs of drug development.[16]

The span of time between new drug discovery and market approval means there could be relatively few years remaining of patent protection by the time the drug reaches the market. This is particularly challenging for orphan drug developers who already face a limited market from which to recover their research costs. As a result, developers can be discouraged from investing in drugs with a potentially limited market value.[17]

3. The ODA

When the ODA was signed into law on January 4, 1983, the United States became the first country in the world to provide incentives for developing treatments for rare diseases.[18,19]

> "I am pleased to sign into law today the Orphan Drug Act…The cost of discovering and developing a new drug is often staggering. By definition, an orphan drug is one that treats a disease that affects 200,000 or fewer individuals – and, from an economic perspective, groups that small do not now justify the kind of research expenditures that companies must make. The bill that I am signing today helps to cure that problem and consequently, we hope, some of the diseases as well. The bill provides incentives for the private sector to develop drugs to treat these rare diseases."[20]
>
> *-President Ronald Reagan,*
> *Statement on signing the Orphan Drug Act*

Since then, Australia, Japan, and the European Union have instituted provisions similar to the ODA to support the development of orphan drugs.[21] The ODA contains a number of provisions designed to encourage investment in orphan drug research and increase the number of drugs available for patients living with a rare disease.

3.1. Becoming an orphan drug

For a drug to qualify for provisions contained in the ODA, it must receive an orphan designation from the FDA. Drug developers may apply for orphan designation at any time before filing an NDA or BLA.[22] The Office of Orphan Products Development within the FDA reviews applications for orphan designation and determines if a drug is eligible to receive the ODTC and other ODA provisions. Receiving an orphan designation does not change the market approval process nor does it imply that the drug will one day reach the marketplace. Orphan designation does make the drug eligible for the benefits created by the ODA, including the ODTC.

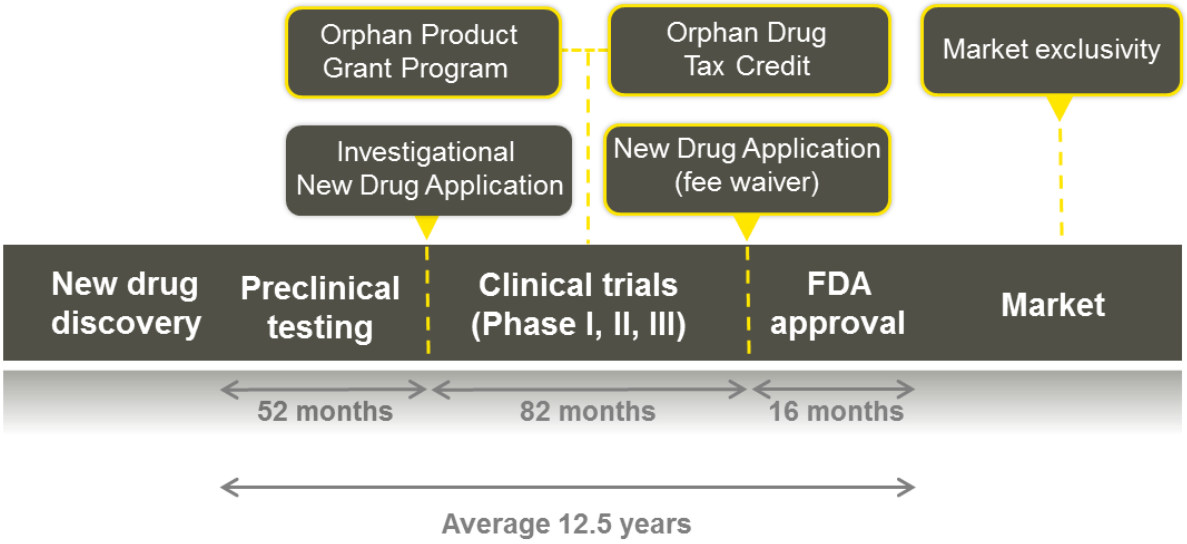
The average review time for an orphan designation is 90 days, and between 60 percent and 70 percent of all applications result in drugs receiving orphan drug status.[23] A drug can only receive orphan designation once it has been determined to diagnose, cure or treat a specific rare disease, defined as affecting fewer than 200,000 people in the United States.

Each orphan drug is approved for specific uses for the treatment of a rare disease. Each of these uses is called an "indication." When granting market approval, the FDA only authorizes a drug for its indication. It is possible for orphan drug developers to obtain a new orphan designation for an existing drug if a new indication or use is found. This encourages developers to seek new ways for existing drugs to be used to benefit patients with rare diseases.

3.2. Major provisions in the ODA

Designated orphan drugs are eligible to receive development assistance under the ODA. Figure 3 adds to the orphan drug timeline the various stages at which the ODA assists developers of orphan-designated drugs.

Figure 3. Available ODA assistance during development timeline for orphan drugs



Source: Joseph A. DiMasi and Henry G. Grabowski, "The cost of biopharmaceutical R&D: is biotech different?" *Managerial and Decision Economics,* (John Wiley & Sons, Ltd, 2007); EY analysis.

From the Orphan Product Grant Program through fee waivers and market exclusivity, the ODA provides incentives designed to encourage additional investment and innovation in the development of innovative treatments for rare diseases. Most provisions in the ODA assist drug developers in the crucial period before their drug reaches the market. The Act was designed this way to encourage innovation and research into treatments for rare diseases by assisting from the earliest stages of development. The broad package of provisions included in the ODA supports innovation throughout the development process.[24]

The major provisions in the ODA include the Orphan Products Grant Program, the ODTC, and market exclusivity:

Orphan Products Grant Program. The Orphan Products Grant Program awards grants to researchers and organizations that develop orphan drugs and other orphan products.[25] The grants are designed to support the clinical development of orphan products, which include not only orphan drugs but biologics, medical devices or medical foods that treat a rare disease. Providing assistance to drug developers during the clinical stage, before their product has market approval, is one way the ODA encourages additional research investment.

The program is administered by the Office of Orphan Products Development, which has received over 1,800 grant applications since its founding.[26] Since 1983, the Orphan Drug Grant Program has funded over 500 studies and helped bring more than 45 orphan products

to market that otherwise may not have been able to attract enough outside investment.[27] The Orphan Products Grant Program awards approximately $14 million for orphan product research grants per fiscal year.[28]

ODTC. The ODTC offers drug developers a tax credit equal to 50 percent of qualified clinical trial costs related to the development of designated orphan drugs. Average out-of-pocket costs incurred by drug developers during the clinical trial phase are $425 million per approved drug, in 2014 dollars.[29] The clinical trial costs covered by the ODTC are a portion of the total cost of bringing a new drug to market.

Like most provisions in the ODA, the ODTC offers assistance before drugs have received market approval. This helps to alleviate some of the risk developers face when making large investments in treatments for rare diseases where the ability to recover their costs from very small patient populations may be uncertain. Because the ODTC is a non-refundable tax credit, pre-market drug developers – those without tax liability – cannot use their ODTC immediately even though they incur the same costs as established developers. However, the ODTC can be carried forward to future tax years until the pre-market drug developer has generated sufficient federal income tax to utilize the tax credit, up to 20 years.

The ODTC encourages additional investment in orphan drug development by reducing the investment barrier – sometimes called the cost of capital – for drug developers. This barrier can be especially large for small, start-up drug developers who often face additional funding constraints.

Market exclusivity. The FDA grants market exclusivity for different periods of time and for one of several reasons, including for an orphan drug, a new chemical, a pediatric application, or

Box1: Examples of orphan drugs developed since the ODTC

Since the ODTC, over 200 new orphan drugs have been made available to treat patients suffering from a rare disease.

Hereditary angioedema (HAE)
HAE is a potentially life-threatening immune system disorder that causes severe swelling of the body, particularly of the hands, face, feet, and airways. Since 2008, there have been four orphan drugs approved to treat HAE attacks.

Cystic fibrosis (CF)
CF is a life-threatening genetic disease that causes damage to the lungs and digestive system. It is estimated that 30,000 people in the United States have CF. There is no cure for CF, although there are four orphan drugs approved to treat certain genetic mutations and symptoms associated with CF; two of these treatments were approved in the last five years.

Childhood acute lymphoblastic leukemia (ALL)
Childhood ALL is a blood and bone marrow cancer. Those with ALL are more susceptible to infections, anemia, and bleeding. ALL is the most common type of childhood cancer, and approximately 3,000 people younger than 20 are diagnosed with ALL each year in the United States. There is only one approved orphan drug to help treat a certain type of ALL.

Sickle cell anemia
Sickle cell disease is a serious condition that affects the shape of red blood cells. It can cause frequent pain and require blood transfusions. There is only one orphan drug available to reduce certain symptoms of certain types of Sickle cell anemia.

a patent challenge. In the case of orphan drugs, market exclusivity is the exclusive right to sell a specific orphan drug for treatment of a specific rare disease. The FDA awards orphan drug developers seven years of market exclusivity, which is intended to provide them the opportunity to recover the significant investment required to bring a drug to market. It is the only major ODA provision to apply after market approval.

Drug patents are granted for 20 years, but, because it takes an average of 12.5 years to complete the FDA drug approval process, orphan drugs can reach the market with relatively few years of patent protection remaining. Market exclusivity extends the time orphan drug developers have to recover their investment. The smaller markets for orphan drugs make it harder for developers to recover costs through sales during the short window of protection granted by a patent. Drugs developed for more common diseases are better able to spread those costs over larger patient populations.

Market exclusivity is designed to balance the need to provide additional incentives for orphan drug development and encourage innovations that benefit patients. Market exclusivity does not prohibit other drug developers from receiving market approval for a different orphan drug for the same condition. In addition, if a new drug is more effective, safer, or provides a major contribution to patient care, it may be introduced even if an earlier drug's market exclusivity is still in effect.

3.3. Other laws that encourage orphan drug production

The ODA provides a set of provisions designed to increase orphan drug production. Other pieces of laws contain rules that are helpful to orphan drug developers, but none specifically target treatments for rare diseases the way the ODA does. Table 1 compares provisions in the ODA to other laws.

Table 1. Laws that encourage additional orphan drug production

	Bayh-Dole Act 1980	Hatch-Waxman Act 1984	FDA Modernization Act 1997	Orphan Drug Act 1983
Market incentives				✓
Reduced FDA review time			✓	
Improved research ownership rules	✓			
Fee waivers				✓*
Encouraged pediatric studies			✓	
Drug development grants				✓
Tax credit				✓
Increased patent term		✓		

Note: * Added as an amendment in 1992.
Source: The Bayh-Dole Act of 1980, the Hatch-Waxman Act of 1984, the FDA Modernization Act of 1997; the Orphan Drug Act of 1983; EY analysis.

The Bayh-Dole Act (1980) updated research ownership rules by allowing researchers funded in part by federal funds or grants to retain ownership of their inventions. In 1984, the Hatch-Waxman Act (also known as the Drug Price Competition and Patent Term Restoration Act) addressed the pharmaceutical industry's problem of shorter effective patent terms by allowing patents to be extended for the number of years the drug is reviewed by the FDA plus half the time the drug is in preclinical trials (maximum extension of 5 years). Longer patent terms incentivize pharmaceutical companies to pursue treatments that might be more costly to develop because they have longer patent terms post-approval to recover their investment. The market exclusivity provision in the ODA follows the same principle by guaranteeing drug developers a fixed length of time to recover their research costs, though unlike the Hatch-Waxman Act, it applies to both patentable and un-patentable drugs.

The FDA Modernization Act of 1997 (FDAMA) includes multiple provisions, but most importantly for orphan drugs, it increased patient access to information about experimental treatments, created an accelerated review process for important medications, and created the Pediatric Exclusivity Extension, which gives developers who conduct pediatric clinical trials an additional six months of market exclusivity.[30] Approximately 50 percent of those affected by rare diseases are children.[31]

As part of its goal to increase access to information, the FDAMA created a data bank with information on clinical trials for serious or life-threatening diseases where patients can see eligibility criteria to participate in clinical trials and contact the sponsor if they wish to participate. This is especially useful for those suffering from a rare disease as it can be difficult to find a sufficient number of participants for clinical trials.[32]

3.4. Amendments to the ODA

Since its enactment in 1983, Congress has repeatedly amended the ODA to include additional incentives and support for orphan drug development. Some changes have simply improved the clarity and focus of the provisions, such as the 1984 amendments to the ODA, which defined rare diseases as affecting fewer than 200,000 patients in the United States. Others have strengthened the original Act, such as by extending market exclusivity to patentable, as well as un-patentable products.[33] Congress waived certain fees for orphan drug developers in 1992, and in 1997 permanently extended the ODTC. According to the FDA, fee waivers for orphan drug developers can total $2 million, which can offer significant assistance, especially for small, pre-market developers.[34]

The permanency of the ODTC may enhance its ability to incentivize additional investments in orphan drugs. Given the long and varied time period required to develop an orphan drug, uncertainty around the ODTC's status could discourage developers from committing to the process. As a result, fewer developers might be willing to invest in research and development if they believed the ODTC was not permanent.

4. Impact of the ODA

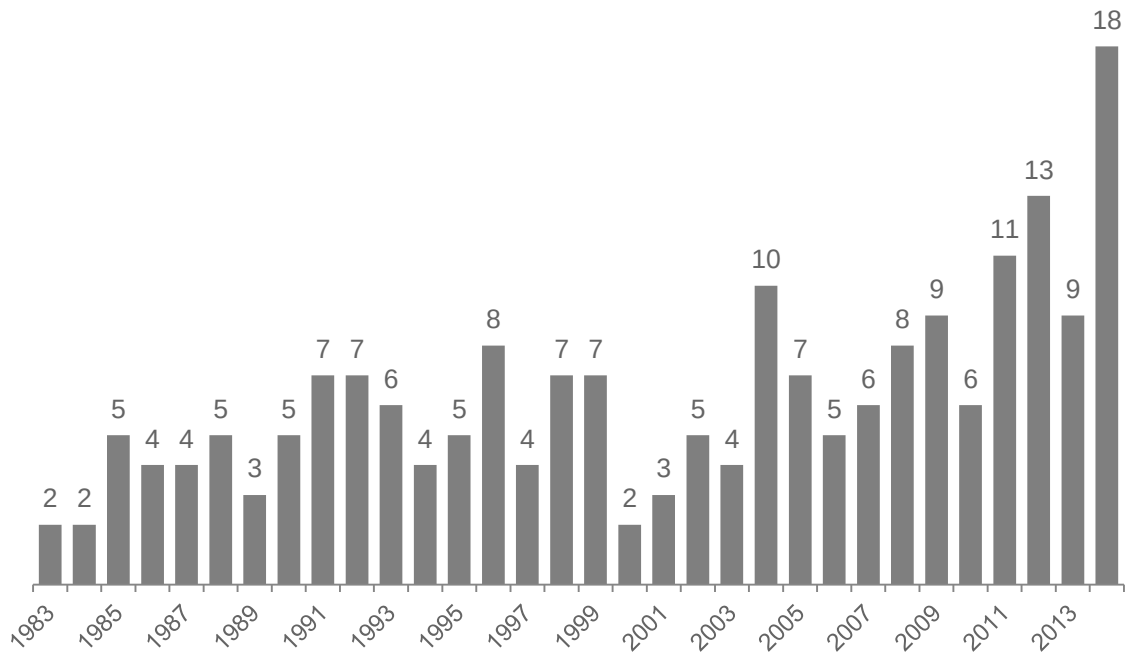
On average, in the decade before the ODA, only two new orphan drugs were produced each year.[35] Post-ODA, there has been a dramatic increase in the number of new orphan drugs brought to market. The number of new orphan drugs in the development pipeline has increased rapidly as well.

> "Enactment of the Orphan Drug Act in 1983 has proved to be a very successful venture in public policy, focusing private dollars and intellect on these vexing and often fatal diseases."[36]
>
> *-Senator Ron Wyden (D-OR), 4 October 1994,*
> *Statement on the introduction of the Office of Rare Disease Research Act*

4.1. Increased production of orphan drugs

Incentives in the ODA have played an important role in the increase in orphan drug production over the last 30 years. Since 1983, 201 new orphan drugs have been brought to market, in part, due to the ODA. The increase in drug innovation and development has been especially strong in recent years, with 18 new orphan drugs approved in 2014.[37] Figure 4 shows the number of new orphan drugs approved since the ODA was enacted.

Figure 4. New orphan drug approvals since ODA enactment



Note: Orphan drug approvals include both new molecular entities (NMEs) and new biologic license applications (BLAs).
Source: Drug Approval Reports, Food and Drug Administration, various years; EY analysis.

The ODA is also used to assist drug developers in the re-development of existing drugs for the treatment of rare diseases or new formulations; which can significantly reduce negative side effects and improve patient welfare. In total, 486 orphan products have been approved

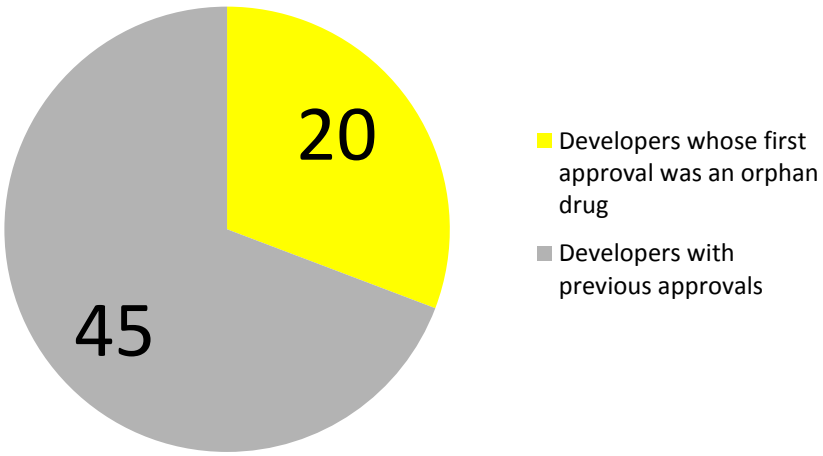
since ODA enactment.[38] This includes a mix of more effective formulations, new indications, dosages, sources of supply, and other changes that have illustrated clinical superiority.[39] While not all approvals represent a new drug, they have the potential to improve outcomes for the patients they were designed to treat.

The development pipeline for new orphan drugs also continues to increase. Between 2004 and 2014, the FDA has awarded nearly 2,000 orphan designations.[40] That includes designations for new drugs, as well as other product improvements or updates.

4.2. Distribution of orphan drug development

Development of new orphan drugs is not concentrated among a few drug developers, but is broadly distributed throughout the industry. Between 2004 and 2014, 65 separate companies received market approval for at least one new orphan drug. For nearly a third of those companies, approval was for their first successful drug brought to market, orphan or otherwise. Figure 5 highlights the distribution of new orphan drug approvals between 2004 and 2014.

Figure 5. Distribution of new orphan drug approvals, 2004-2014



Source: Drug Approval Reports, Food and Drug Administration, various years; EY analysis.

Data from the FDA suggests that both small and large drug developers pursue orphan drug research. For some developers, all or almost all of their drug approvals are for orphan drugs. ODA provisions are particularly important to the often small developers who specialize in orphan drug development.

5. Impact of the ODTC

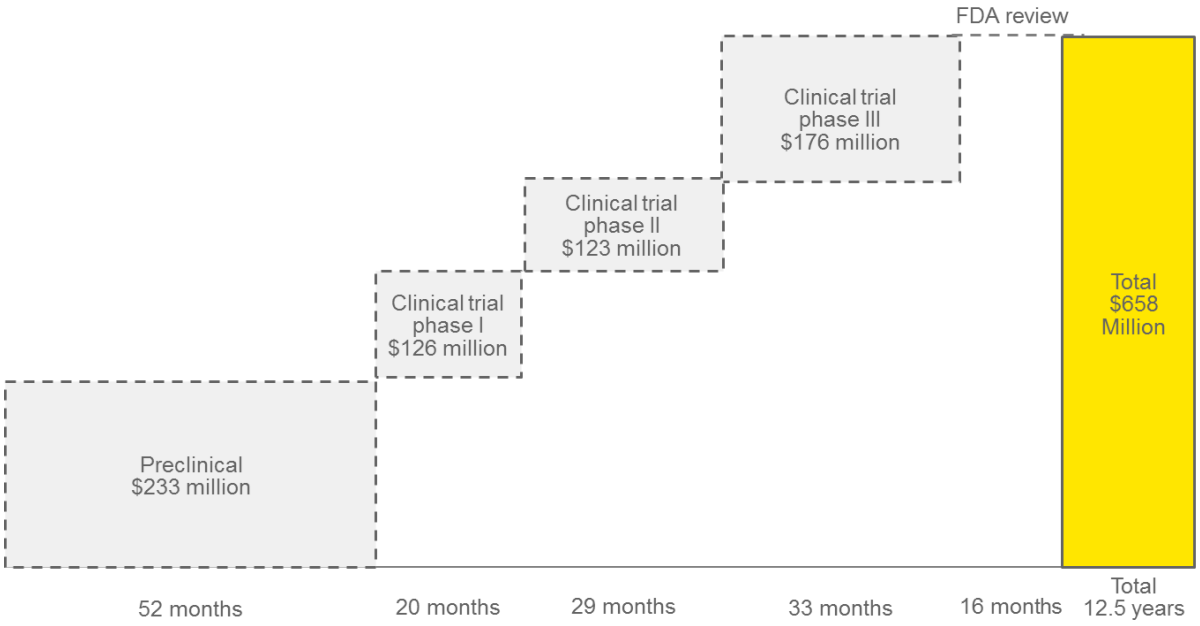
A central provision of the ODA is the ODTC, which allows orphan drug developers to receive a tax credit for a portion of their clinical trial costs. The ODTC provides an incentive for drug developers to invest additional resources in orphan drug development. The ODTC reduces the size of the investment barrier – sometimes called the cost of capital – for drug developers.

> "Few provisions of the tax code can claim to have clearly reduced human suffering and to have expanded our store of medical knowledge. This credit has done both."[41]
>
> *-Senator Orrin Hatch (R-UT), 20 July 1995,*
> *Statement on 1995 amendment to the Orphan Drug Act*

5.1. Overview of the ODTC

The ODTC allows orphan drug developers to claim a tax credit for up to 50 percent of qualified clinical testing expenses. Clinical testing costs are a subset of the total cost to bring a new drug to market. Qualified expenses for the ODTC include certain human clinical testing costs incurred between orphan designation and drug approval.[42] Figure 6 shows the average length and out-of-pocket costs per approved drug for each phase based on research by the Tufts Center for the Study of Drug Development.[43] Values in Figure 6 are representative of what the average drug costs to develop and do not reflect the costs of any particular drug. The out-of-pocket costs are a subset of the total cost – $1.5 billion in 2014 dollars – of bringing a new drug to market because they do not include the cost of capital associated with drug development.

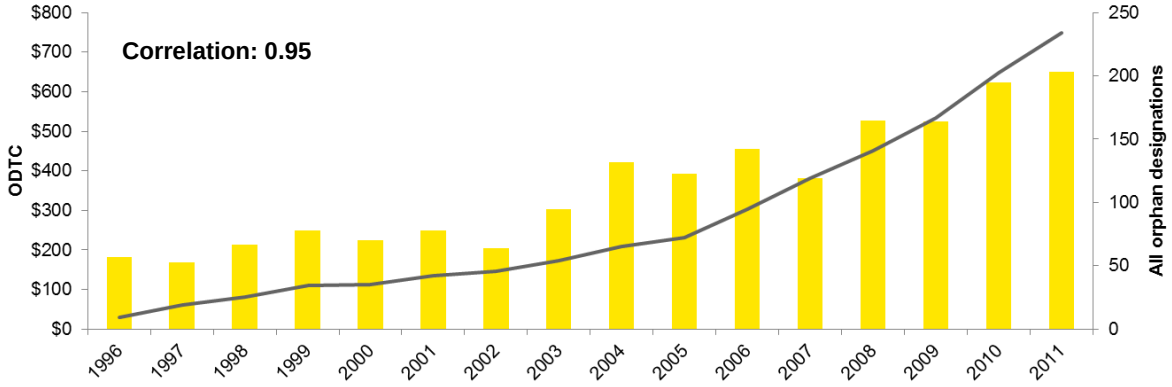
Figure 6. Average out-of-pocket costs per approved drug (in 2014 dollars)



Source: Joseph A. DiMasi and Henry G. Grabowski, "The cost of biopharmaceutical R&D: is biotech different?" *Managerial and Decision Economics,* (John Wiley & Sons, Ltd, 2007); EY analysis.

The ODTC covers expenses related to human clinical testing conducted outside the United States only if an insufficient population of test participants exists domestically. Qualified expenses for the ODTC cannot be used toward the research (R&D) tax credit.[44] For rare diseases, clinical trial costs alone can total thousands of dollars per person diagnosed with the disease. Between 1996 and 2011, the amount of ODTC awarded to orphan drug developers increased from $31 million to over $750 million (Figure 7).

Figure 7. Total ODTC awarded, in millions of USD



Note: All designations include NMEs, new BLAs, and other orphan designations, such as new indications, formulations, and dosages.
Source: Orphan Drug Product designation database, Food and Drug Administration; Statistics of Income, Internal Revenue Service; EY analysis.

5.2. ODTC case studies

To illustrate how the ODTC lowers the cost of developing new treatments for rare diseases and how it interacts with the R&D tax credit, two quantitative case studies are presented. The first is for an established drug developer with a portfolio of drugs currently on the market that provide sufficient income to fund development of a new orphan drug. The second is for a pre-market company developing its first drug and relying on investors to cover its drug development costs for the 12 or more years needed to bring the orphan drug to market.

Case study 1: Established drug developer. This quantitative case study calculates the benefit of the ODTC for an established drug developer. An established developer is one with prior drug approvals and tax liability. Established developers are able to use the ODTC to reduce their federal income tax liability. They can use the ODTC to offset development costs in the same year the costs are incurred. For research and development costs not covered by the ODTC, the R&D tax credit may be used; however, it typically provides a more limited benefit for orphan drug developers.

Table 2 shows each stage of drug development and associated average lengths and costs. It also shows the tax credit the company is allowed to claim at each stage. The ODTC allows developers to claim a tax credit for 50 percent of eligible costs. For development stages that do not qualify for the ODTC, the company can claim the R&D tax credit. The calculation of the allowed R&D tax credit can be complex and company-specific. For the purpose of the

case studies presented in Table 2 and Table 3, the R&D tax credit is assumed to cover six percent of eligible drug development expenses.[45]

Table 2 displays the out-of-pocket costs of drug development under two tax policy scenarios – with and without the ODTC. With the ODTC, the established drug developer is able to claim the R&D tax credit for expenses related to the "Preclinical" stages and the ODTC for the three phases of clinical trials. The value of these credits in the "With the ODTC" scenario is shown in the shaded columns of Table 2. Without the ODTC, the established drug developer would be able to claim the R&D tax credit for those expenses that would otherwise have been covered by the ODTC.

Table 2: Case study - Established drug developer

Development stage	Average length (months)	Out-of-pocket costs (in millions)	With the ODTC		Without the ODTC	
			R&D Credit	ODTC	R&D Credit	ODTC
Research and preclinical	52	$233.0	-$14.0		-$14.0	
Clinical						
Phase I	20	$125.6		-$62.8	-$7.5	
Phase II	29	$122.7		-$61.4	-$7.4	
Phase III	33	$176.2		-$88.1	-$10.6	
FDA approval	16					
Total present value		$466.3	-$11.3	-$138.8	-$28.0	
Net out-of-pocket costs			**$316.1**		**$438.3**	

Note: The discount rate used in the case study is based on the long-run term Treasury bill rate estimated by the Congressional Budget Office and is set to 5 percent.
Source: Congressional Budget Office; EY analysis.

The "Total present value" row shows the value of these costs and credits when taking into account the time-value of money and the company's cost of capital. Drug development is a series of long-term investments, and companies must be able to fund them over long periods before receiving any kind of return on those investments from drug sales, licensing, or other sources. The present value calculation takes these factors into account, which has the effect of increasing the relative value of costs and credits earlier in the process and decreasing the relative value of those that occur later in the process.

In the policy scenario with the ODTC, the established drug company is able to claim R&D tax credits with a present value of $11.3 million and ODTCs with a present value of $138.8 million. In the policy scenario without the ODTC, the value of the ODTC drops from $138.8

million to zero and the R&D tax credit increases from $11.3 million to $28.0 million. The increased R&D tax credit would be about one-tenth of the lost ODTC.

The “Net out-of-pocket costs” row shows the present value of the out-of-pocket costs less the present value of the tax credits received. For the policy scenario with the ODTC, the cost for an established drug developer to develop a new drug is reduced from $466.3 million to $316.1 million. For the scenario without the ODTC, the available R&D tax credits would reduce the cost to develop a new drug from $466.3 million to $438.3 million.

For this established drug developer, the ODTC lowers the net out-of-pocket cost of developing a new orphan drug by $122.2 million (the difference between the two policy scenarios). By reducing the cost of development by more than one-third, the ODTC helps developers to recoup their investment in orphan drug research. The additional research investment generated by the ODTC is expected to lead to future increases in the number of new orphan drugs available for patients suffering from a rare disease.

Case study 2: Pre-market drug developer. This quantitative case study calculates the benefit of the ODTC for a pre-market drug developer. A pre-market developer is one without prior drug approvals and no expectation of having tax liability in the near future.

Box 2: Impact of potential repeal of the ODTC

If the ODTC were repealed, the net out-of-pocket cost of orphan drug development would increase by:

+39 percent for established drug developers

+30 percent for pre-market drug developers

Pre-market developers cannot use their ODTCs (or other nonrefundable credits like the R&D tax credit) until they have tax liability that the credits will reduce. Even though pre-market developers incur the same costs as established developers, they must wait – sometimes more than 12 years – to receive the benefits of the ODTC or other tax incentives. As a result, pre-market developers realize fewer tax benefits than more established developers. The fact that pre-market companies must wait longer to benefit from the tax credits is reflected in Table 3. The value of tax credits is shown in gray in the year they are earned and in black when the company can use them.

The pre-market company claims the same amount of tax credits as the established drug developer shown in Table 2. The present value of the tax credits, however, is lower for the pre-market company because it has to wait longer before it can use the tax credits.

Table 3: Case study - Pre-market drug developer

Development stage	Average length (months)	Out-of-pocket costs (in millions)	With the ODTC		Without the ODTC	
			R&D Credit	ODTC	R&D Credit	ODTC
Research and preclinical	52	$233.0	-$14.0		-$14.0	
Clinical						
Phase I	20	$125.6		-$62.8	-$7.5	
Phase II	29	$122.7		-$61.4	-$7.4	
Phase III	33	$176.2		-$88.1	-$10.6	
FDA approval	16					
Post-market	150+		-$14.0	-$212.3	-$39.5	
Total present value		$466.3	-$7.6	-$115.5	-$21.5	
Net out-of-pocket costs			**$343.2**		**$444.8**	

Note: The discount rate used in the case study is based on the long-run term Treasury bill rate estimated by the Congressional Budget Office and is set to 5 percent. The value of tax credits is shown in gray in the year they are earned and in black when the company can use them.
Source: Congressional Budget Office; EY analysis.

For this pre-market drug developer, the ODTC lowers the net out-of-pocket cost of developing a new orphan drug by $101.6 million. This is nearly $21 million less than what an established developer would have received.

This is not to imply that the ODTC is not valuable for pre-market companies. In the absence of the ODTC, the net out-of-pocket cost to a pre-market company of developing an orphan drug would increase by 30 percent. The fact that established drug developers would see an increase of 39 percent does not in any way diminish the magnitude of the challenge that pre-market companies would face in the absence of the ODTC.

Pre-market companies can also benefit from the ODTC through partnerships and mergers and acquisitions (M&A) with established companies. The ODTC increases the value of pre-market companies' R&D investments related to rare diseases. Potential acquirers may be willing to pay more for pre-market companies when they have accumulated tax credits that the acquirer may be able to use.[46]

Not all pre-market companies fund the development of their drugs through to the end of the approval process. Many companies will license or sell the rights to their drugs to established drug developers that may have better access to the capital and expertise needed to manage the final stages of the development process. Even if the pre-market company is not the one

that ultimately earns the ODTC, the fact that they have developed a promising drug that will qualify for the ODTC increases the amount the pre-market company can demand to license its discovery.[47]

5.3. Quantifying the effect of repealing the ODTC

The ODTC assists drug developers by reducing the cost of investment to research and develop a new orphan drug. By lowering the cost of capital for orphan drug developers, the ODTC attracts additional investment to orphan drug development activities. While not every new drug is successful, additional investment can be expected to lead to an increase in approved orphan drugs over time. Figure 8 graphically represents the primary economic links between the ODTC and new orphan drugs.

Figure 8. Process of increasing orphan drug production

Source: EY analysis.

The effect of the ODTC on the cost of capital for a drug developer can be calculated using a methodology sometimes used by the Joint Committee on Taxation and the US Treasury Department to evaluate the impacts of the tax system on investment incentives. The cost of capital framework accounts for the major features of the income tax affecting investment, including the corporate income tax rate, capital cost recovery, the tax treatment of debt versus equity financing, R&D expensing, tax credits, industry structure, inflation, and the ODTC. Once the impact on the cost of capital is calculated, it can be combined with the sensitivity of industry investment to changes in its tax treatment.

Before a company can make a major new investment in R&D or in another investment project, it needs to raise the required capital. Whether capital comes in the form of debt or equity, investors will expect to be paid a financial return on the capital they provide. The return a company needs to provide investors in order to raise the capital is known as the company's "cost of capital." Investments that do not produce a large enough return to cover their required cost of capital or "hurdle rate" will generally not be made. For this reason, companies generally do not invest in projects that are not expected to cover their cost of capital. Taxes raise a company's cost of capital because the company has to earn more to cover its taxes and still pay a competitive return to its investors.

Measuring the responsiveness of investment to changes in tax policy – often called the investment elasticity – is the subject of a large body of academic literature. Numerous studies have found a significant relationship between the cost of capital and the level of investment.[48] All else equal, assets of an industry with a lower cost of capital will attract more investment than those with a higher cost of capital. The same is true for orphan drug

development, which is why the ODTC was designed to reduce the cost of capital for investment in orphan drugs.

5.4. Impact of the ODTC on the cost of capital

The cost of clinical trials is a qualified expense for purpose of the ODTC. If the ODTC were repealed, drug developers would instead likely claim the R&D tax credit for their clinical trial costs. This analysis assumes that development costs incurred during the discovery and preclinical phases (which are not qualified expenses for purpose of the ODTC) are eligible for the R&D tax credit.

An important factor in determining the cost of capital for drug developers is the length of time associated with each stage of development. As shown in Figure 6, drug development can be a lengthy process and the average development time of an approved drug takes an average of 12.5 years. As a result, the R&D tax credit and ODTC claimed during different phases of drug development provide different benefits when considered in terms of present value.

Box 3: Impact of repealing the ODTC

If the ODTC were repealed, investment in orphan drug development would decline by:

-36.3 percent for established drug developers

-27.0 percent for pre-market drug developers

Established drug developers with tax liability have access to all of their credits in the same year development costs are incurred. Pre-market drug developers (those without tax liability) must wait until they have tax liability, usually after drug approval, to use their credits. The present value of the tax credits is lower for the pre-market company because they have to wait longer before they can use the tax credits.

Table 4. Estimated percent increase in the cost of capital from potential repeal of the ODTC using different assumptions for the cost and length of drug development

Parameter source	Established	Pre-market
DiMasi (2003)	39.5%	27.7%
DiMasi (2007)	36.2%	25.4%
Fagnan (2013)	33.1%	28.0%
Average	**36.3%**	**27.0%**

Note: The percent increases are estimated using the different assumptions for the cost and length of drug development phases reflected in each of the three studies cited.
Source: DiMasi (2003), DiMasi (2007), Fagnan (2013); EY analysis.[49]

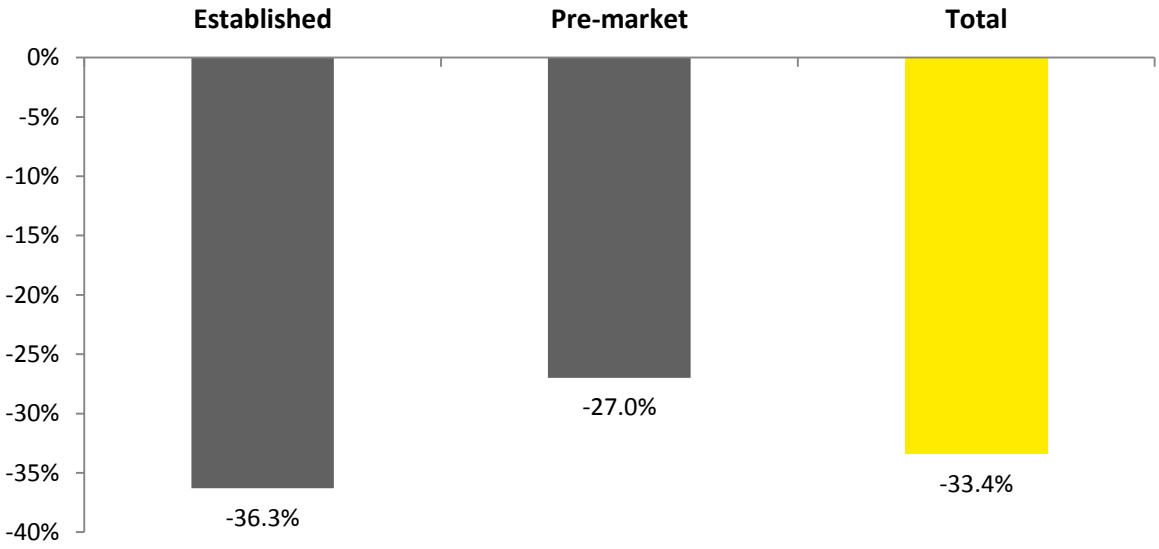
The academic literature contains a range of estimates for the costs and timeline for new drug development. These parameters are entered into the cost-of-capital calculation to estimate the effect that repeal of the ODTC would have on the cost of capital for new orphan drug development. This report uses the average estimated change in cost of capital from the academic studies listed in Table 4.[50]

5.5. ODTC and drug development investment

Based on a review of the economic research that examines the responsiveness of R&D spending to its tax treatment, the long-run responsiveness of R&D investment to its cost of capital is approximately one, meaning that for every one-percent increase in the cost of capital, research investment will fall by one percent.[51]

Applying these estimates of the long-run responsiveness of R&D spending to its tax treatment suggests that if the ODTC were repealed, investment in orphan drug development would decline by 36.3 percent and 27.0 percent for established and pre-market drug developers, respectively (Figure 9). The reduction in investment could be expected to reduce the number of new orphan drugs in the future. As fewer orphan drugs enter the development pipeline, the number of orphan drug approvals would also likely decline.

Figure 9. Estimated decline in research and development investment in orphan drugs, by type of developer under potential ODTC repeal



Source: EY analysis.

As shown in Figure 5, 20 of the 65 orphan drug developers were in the pre-market stage when they received their first orphan drug approval. Therefore, the analysis assumes that 31 percent of orphan drug development investment is attributable to the pre-market drug developers, which results in an estimated industry-wide decline in investment of 33.4 percent. Figure 9 shows the estimated decline in investment for established and pre-market drug developers, as well as the industry wide decline.

5.6. Potential impact of repealing the ODTC

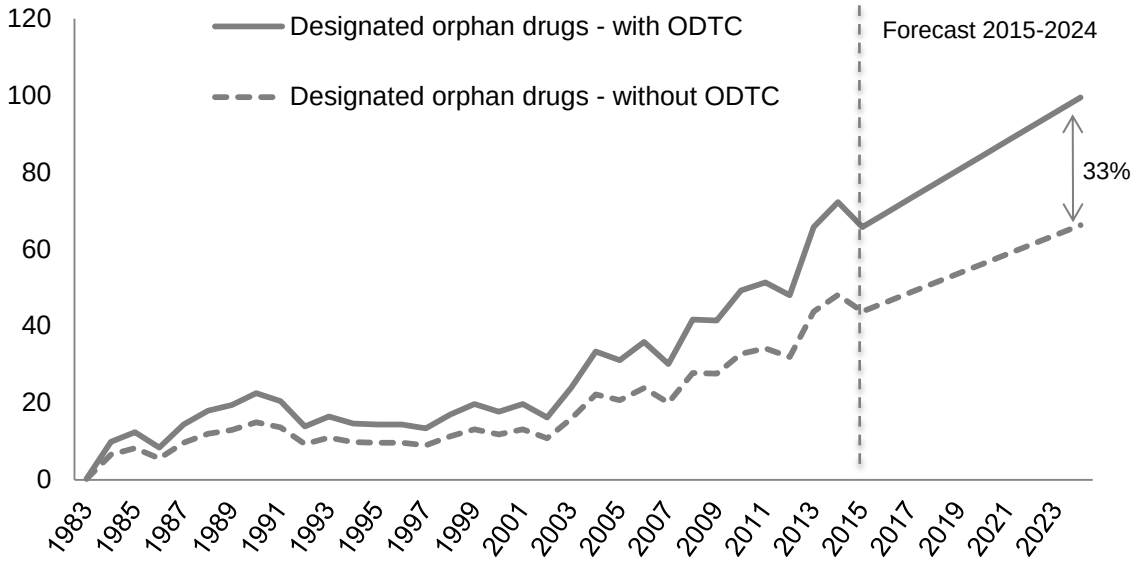
This analysis assumes that a decline in the level of investment in orphan drug research would lead to a proportional decline in the number of new orphan drugs entering the development pipeline and, eventually, to fewer orphan drugs on the market. Figures 10 and 11 show the estimated impact on the orphan drug pipeline and the number of orphan drug

approvals over the 1983 through 2014 period both under current law and assuming the ODTC were not enacted and/or were repealed.

Had the ODTC not been enacted as part of the ODA, this analysis estimates that 277 orphan drugs (33 percent) would not have begun development from 1983 to 2014 (i.e., the dashed line in Figure 10). Without the ODTC, those drugs would not have been able to attract sufficient investment and would have been similar to the treatments for rare diseases that were "orphaned" prior to the passage of the ODA and ODTC.

The analysis uses the historical growth rates to project the number of new orphan drugs likely to enter the pipeline from 2015 through 2024. Based on this approach, it is estimated that 276 fewer orphan drugs would enter the development pipeline over the next 10 years absent the ODTC. The decrease in orphan designations is notable because they are indicative of the development pipeline for future orphan drugs.

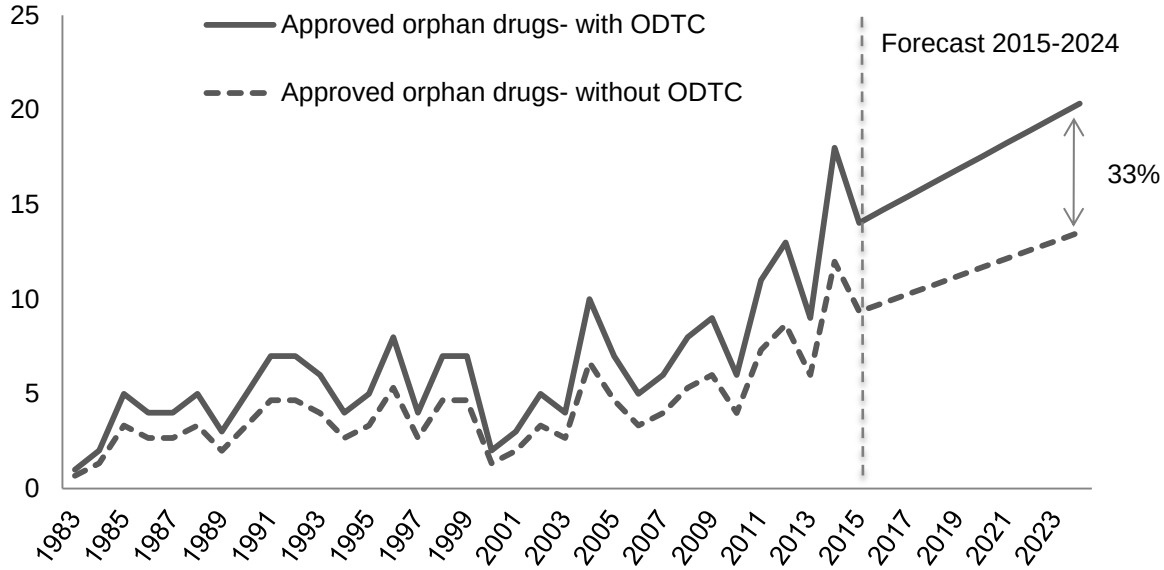
Figure 10. Estimated impact of potential ODTC repeal on the orphan drug pipeline



Note: Projection beyond 2014 is based on the annual average change in orphan drug NME and new BLA approvals from 2004 to 2014 with and without the ODTC.
Source: Drug Approval Reports, Food and Drug Administration, various years; EY analysis.

Figure 11 shows the number of new orphan drugs receiving FDA approval every year from 1983 to 2014 assuming approvals decline proportionally with the estimated decline in designations and underlying investment. The historical growth rates are used to project likely future approvals from 2015 through 2024. In 2014, the FDA approved more new drugs – orphan or otherwise – than at any time during the previous decade.[52] Since the ODA was passed, the FDA has approved over 200 orphan drugs.

Figure 11. Estimated impact of potential ODTC repeal on new orphan drugs



Note: Projection beyond 2014 is based on the annual average change in orphan drug NME and new BLA approvals from 2004 to 2014 with and without the ODTC.
Source: Drug Approval Reports, Food and Drug Administration, various years; EY analysis.

The dashed line in the Figure 11 indicates the estimated number of approved orphan drugs had the ODTC not been enacted. From 1983 through 2014, it is estimated that 67 fewer approved orphan drugs (33 percent) would be on the market without the ODTC. This analysis estimates that 57 fewer orphan drugs would be approved over the next 10 years if the ODTC were repealed.

6. Qualitative impact of the ODTC

Repeal of the ODTC would have a direct impact on orphan drug development and the number of new orphan drugs approved in the future, as discussed in the previous section. Patients can benefit from orphan drugs through longer life spans and higher quality of life, while society as a whole can benefit from increased patient productivity and a potential decline in the amount of resources devoted to health care and government spending.

6.1. Impact of orphan drugs on patients' lives

Orphan drugs can affect both the length and the quality of patients' lives. Although the quality of life can be difficult to measure, it is an important part of the benefit that orphan drugs provide.

Longevity. Effective orphan drugs can extend and improve patients' lives. Prior to the ODA, the number of annual deaths from rare diseases was growing at a slightly higher rate than that from other diseases (2.0 percent and 1.3 percent, respectively).[53] In the 10 years following the ODA, the number of annual deaths from rare diseases was declining at a rate of 3.1 percent, while the annual number of deaths from other diseases continued to grow at a rate of 1.2 percent.[54] While the ODA is not the sole reason the annual deaths from rare diseases have declined, it has led to the development of additional orphan drugs, which have played a role in reducing annual deaths from rare diseases.

Quality of life. Orphan drugs have the potential to generate large improvements in patients' lives because rare diseases typically have few, if any, effective treatments available. According to the Office of Rare Diseases Research at the National Institutes of Health, only 289 of the more than 7,000 identified rare diseases have at least one treatment option. That means only four percent of recognized rare diseases have an available treatment, despite the large improvement in the lives of patients and their caregivers provided by a single treatment.[55]

A recent survey, conducted by the biotechnology company Shire, found that rare diseases take a significant emotional toll on patients and their caregivers. Patients and caregivers reported suffering from isolation from friends and/or family (65 percent and 64 percent), depression (75 percent and 72 percent), and anxiety and stress (86 percent and 89 percent).[56] Patients often have to travel long distances to receive treatment. On average, it takes 7.6 years for rare-disease patients in the United States to receive an accurate diagnosis, and patients may see up to four primary care doctors and four specialists before receiving an accurate diagnosis.[57] Orphan drugs may reduce the emotional toll patients and caregivers face by relieving symptoms and decreasing the burden of inferior treatment options. These improvements may help reduce feelings of depression, isolation, anxiety, and stress patients and caregivers often experience.

6.2. Economic impact of orphan drugs

Orphan drugs can also deliver a broad set of economic benefits beyond the increased well-being of patients and caregivers. Orphan drugs may increase patients' ability to work, reduce net medical expenditures, and lower government spending.

Patient and caregiver productivity. Those suffering from chronic disease tend to be less productive at work, either through increased absenteeism or limitations imposed by their disease.[58] Patients with rare diseases often find it difficult to remain at their jobs due to the symptoms of their disease.[59] Labor-force participation generates personal income and increases government revenues through tax receipts. As a result, treatments that help patients to return to work, provide childcare, or participate in other activities may generate benefits beyond improved health.

The adverse effects of rare diseases are not limited to patients but can affect caregivers as well. Those caring for someone with a rare disease report feelings of depression, anxiety and isolation.[60] Treatments that help patients to return to work may also lead to productivity improvements for caregivers.

Health care consumption. Many rare diseases are classified as severe, which require more paid and unpaid care than non-severe diseases.[61] Those with debilitating conditions often require in-home residential care, which can be expensive. Patients with less severe conditions may still need a family or friend to be present and able to help in case of an emergency.

Health care costs for patients with a rare disease can be substantial. Having an effective treatment available can reduce the need to see numerous doctors, specialists, and undergo multiple tests. Compared to patients with more common diseases, rare disease patients see more doctors and have more diagnostic tests, all of which drive up health care consumption. High levels of health care consumption increase pressure on the US health care system and place a higher financial burden on insurance companies and patients. In a recent survey, 55 percent of respondents incurred medical expenses not covered by insurance (90 percent reported having insurance).[62] Effective treatments for rare diseases may lower total out-of-pocket cost medical costs for patients and reduce the aggregate level of health care consumption.

Government spending. New drugs have been shown to reduce total medical expenditures, potentially reducing government expenditures.[63] Research in this area that focuses on rare diseases is limited. One study conducted on patients with Parkinson's disease who took the drug Selegiline found that the drug may reduce government spending by $10 million per week by delaying the need for disability payments and providing tax revenues while patients continue to work.[64] New orphan drugs may generate similar outcomes and reduce government spending for patient populations with rare diseases.

7. Conclusion

The ODA, and more specifically the ODTC, have made significant contributions to the increase in orphan drug discovery over the last 30 years. Without the ODA, market and regulatory barriers would limit investment in finding new, potentially life-saving treatments for patients living with rare diseases. Drug developers use the ODTC to help finance investments in developing potential new treatments.

When Congress passed the ODA, it was concerned that rising development costs had caused promising medicines to be abandoned without reaching patients. Today, the total cost to bring a new drug to market is $1.5 billion (in 2014 dollars). Lacking sufficient market size or economic incentive, new treatments might not be developed to treat rare diseases. ODA provisions, like the Orphan Products Grant Program and the ODTC, were designed specifically to combat such barriers and increase orphan drug development.

In response, drug developers have increased the level of investment in the research and development of new orphan drugs. Since the ODA's enactment, in total, 486 orphan products have been approved and more than 200 new orphan drugs have been brought to market and many more remain in the development pipeline. Both large and small drug developers use provisions of the ODA and ODTC to reduce costs associated with developing new treatments for rare diseases.

This analysis finds that there would have been 33 percent fewer new orphan drugs developed during the last 30 years without the ODTC. That is the equivalent of 67 drugs, currently on the market, that would not have been developed. The ODTC has also been used to begin development on a number of new drugs that may ultimately receive market approval. Without the ODTC, it is estimated that the drug development pipeline would ultimately shrink by 276 developmental drugs over the next 10 years. It is estimated that this reduced pipeline could ultimately result in 57 fewer approved drugs available to patients over the next 10 years.

Both the ODA and the ODTC have largely accomplished Congress' intent to increase orphan drug development. Amendments to the ODA over time have further improved the ability of the ODA and the ODTC to reduce barriers to orphan drug development.

Appendix A: Rare diseases with at least one FDA-approved treatment[65]

Acquired hypoprothrombinemia
Acral lentiginous melanoma
Acromegaly
Acute intermittent porphyria
Acute lymphoblastic leukemia
Acute lymphoblastic leukemia, childhood
Acute myeloid leukemia, adult
Acute promyelocytic leukemia
Adenosine deaminase deficiency
Adult-onset citrullinemia type II
Alpha 1-antitrypsin deficiency
Alveolar capillary dysplasia
Amebiasis
Amyotrophic lateral sclerosis
Amyotrophic lateral sclerosis type 10
Amyotrophic lateral sclerosis type 11
Amyotrophic lateral sclerosis type 2
Amyotrophic lateral sclerosis type 3
Amyotrophic lateral sclerosis type 4
Amyotrophic lateral sclerosis type 5
Amyotrophic lateral sclerosis type 6
Amyotrophic lateral sclerosis type 7
Amyotrophic lateral sclerosis type 8
Amyotrophic lateral sclerosis type 9
Anaplastic large cell lymphoma
Anterior uveitis
Anthrax
Aortic aneurysm, familial thoracic 4
Aplastic anemia
Arginase deficiency
Argininosuccinic aciduria
Atypical hemolytic uremic syndrome
Autosomal recessive juvenile Parkinson disease
Barrett syndrome
B-cell lymphomas
Bidirectional tachycardia
Blepharospasm
Botulism
Carbamoyl phosphate synthetase 1 deficiency
Carcinoid syndrome
Carcinoid tumor
Cardiomyopathy due to anthracyclines
Catecholaminergic polymorphic ventricular tachycardia
CDK4 linked melanoma
Cerebellar ataxia and hypogonadotropic hypogonadism
Chang Davidson Carlson syndrome
Char syndrome
Chromophil renal cell carcinoma
Chromophobe renal cell carcinoma
Chronic granulomatous disease
Chronic Infantile Neurological Cutaneous Articular syndrome
Chronic inflammatory demyelinating polyneuropathy
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Chronic myeloproliferative disorders
Chudley Rozdilsky syndrome
Citrullinemia type I
Classic Kaposi sarcoma
Clear cell renal cell carcinoma
Coccidioidomycosis
Congenital antithrombin deficiency
Congenital antithrombin deficiency type 2
Congenital antithrombin deficiency type 3
Congenital aplastic anemia
Congenital generalized lipodystrophy type 1
Congenital generalized lipodystrophy type 2
Congenital generalized lipodystrophy type 4
Congenital herpes simplex
Congenital sucrase-isomaltase deficiency
Crohn's disease
Cryopyrin-associated periodic syndrome
Cryptococcosis
Cryptosporidiosis
Cushing's syndrome
Cutaneous T-cell lymphoma
Cystic fibrosis

Cysticercosis
Cystinosis
Cystinuria
Cytomegalovirus retinitis
Dermatofibrosarcoma protuberans
Diffuse gastric cancer
Disseminated infection with mycobacterium avium complex
Dopamine beta hydroxylase deficiency
Dystonia 1
Dystonia 2, torsion, autosomal recessive
Dystonia 7, torsion
Endemic Kaposi sarcoma
Esophageal cancer
Esophageal varices
Essential thrombocythemia
Ewing's family of tumors
Ewing's sarcoma
Fabry disease
Factor VII deficiency
Factor XIII deficiency
Fallopian tube cancer
Familial cold autoinflammatory syndrome
Familial colorectal cancer
Familial isolated hyperparathyroidism
Familial Mediterranean fever
Familial myelofibrosis
Familial prostate cancer
Familial renal cell carcinoma
Familial ventricular tachycardia
Fibrinogen deficiency, congenital
Fibrolamellar hepatocellular carcinoma
Focal dystonia
Gastrointestinal Stromal Tumors
Gaucher disease
Gaucher disease type 1
Glanzmann thrombasthenia
Glioblastoma
Glioma
Glycogen storage disease type 2
Gorlin Chaudhry Moss syndrome
Granulomatosis with polyangiitis (Wegener's)
Growth hormone deficiency
Growth hormone insensitivity with immunodeficiency
Hairy cell leukemia
Hansen's disease
Hemangioma
Hemolytic uremic syndrome, atypical, childhood
Hemophilia A, acquired
Hemophilia A, congenital
Hemophilia B
Heparin-induced thrombocytopenia
Hepatic encephalopathy
Hereditary angioedema
Hereditary diffuse gastric cancer
Hereditary leiomyomatosis and renal cell cancer
Herpes simiae (B virus)
Herpes simplex encephalitis
Herpes zoster oticus
Herpesvirus simiae B virus
Hodgkin lymphoma
Homocysteinemia due to MTHFR deficiency
Homocystinuria due to CBS deficiency
Homocystinuria due to defect in methylation cbl e
Homocystinuria due to defect in methylation cbl g
Huntington disease
Hurthle cell thyroid cancer
Hydatidosis
Hypereosinophilic syndrome
Hyperparathyroidism, neonatal severe primary
Hyperparathyroidism, primary
Hypogonadotropic hypogonadism without anosmia, X-linked
Hypothalamic dysfunction
Idiopathic pulmonary fibrosis
Idiopathic thrombocytopenic purpura
Infantile apnea
Interstitial cystitis
Intraocular melanoma
Japanese encephalitis
Juvenile idiopathic arthritis

Kallmann syndrome 2
Kallmann syndrome 3
Kidney cancer
Laron syndrome
Leishmaniasis
Lennox-Gastaut syndrome
Lentigo maligna melanoma
Leukemia, B-cell, chronic
Liver cancer
Lymphoblastic lymphoma
Lynch syndrome
Malaria
Malignant hyperthermia
Malignant melanoma, childhood
Malignant mesothelioma
Mantle cell lymphoma
Mastocytosis
Mastocytosis cutaneous with short stature conductive hearing loss and microtia
Melanoma astrocytoma syndrome
Melanoma, familial
Methylmalonic acidemia with homocystinuria
Methylmalonic aciduria with homocystinuria cbl f
Methylmalonicacidemia with homocystinuria cbl d
Microscopic polyangiitis
Morquio syndrome A
Muckle-Wells syndrome
Mucopolysaccharidosis type I
Mucopolysaccharidosis type II
Mucopolysaccharidosis type VI
Multicentric Castleman's Disease
Multiple endocrine neoplasia type 2A
Multiple myeloma
Multiple sclerosis
Multiple system atrophy (MSA) with orthostatic hypotension
Mycosis fungoides
Myelodysplastic syndromes
Myelodysplastic/myeloproliferative disease
Myelofibrosis
Myopathic carnitine deficiency
N-acetylglutamate synthetase deficiency
Narcolepsy
Natal teeth, intestinal pseudoobstruction and patent ductus
Nephropathic cystinosis
Neuroblastoma
Nodular melanoma
Non 24 hour sleep wake disorder
Non-small cell lung cancer, childhood
Noonan syndrome 1
Ocular melanoma
Ornithine transcarbamylase deficiency
Oslam syndrome
Osteopetrosis
Osteopetrosis and infantile neuroaxonal dystrophy
Osteopetrosis autosomal dominant type 1
Osteopetrosis autosomal dominant type 2
Osteopetrosis autosomal recessive 3
Osteopetrosis autosomal recessive 5
Osteopetrosis autosomal recessive 7
Osteosarcoma
Ovarian cancer
Ovarian epithelial cancer
Paget disease of bone
Paget disease of bone, familial
Pancreatic cancer
Panuveitis
Papillary renal cell carcinoma
Parathyroid carcinoma
Parkinson disease
Parkinson disease type 3
Parkinson disease type 9
Paroxysmal nocturnal hemoglobinuria
Patent ductus arteriosus
Pediatric Crohn's disease
Pediatric hypertension
Pediatric ulcerative colitis
Peripheral T-cell lymphoma
Phenylketonuria
Pheochromocytoma

Pheochromocytoma, childhood
Pheochromocytoma-islet cell tumor syndrome
Philadelphia-negative chronic myeloid leukemia
Pneumocystic carinii pneumonia
Polycythemia vera
Prader-Willi syndrome
Precocious puberty
Premature aging Okamoto type
Primary biliary cirrhosis
Primary carnitine deficiency
Primary gastrointestinal melanoma
Primary malignant melanoma of the cervix
Primary malignant melanoma of the conjunctiva
Protein C deficiency
Pulmonary arterial hypertension
Pure autonomic failure
Renal cell carcinoma 4
Respiratory distress syndrome, infant
ROHHAD
Severe combined immunodeficiency
Short bowel syndrome
Sickle cell anemia
Sjogren syndrome
Slti Salem syndrome
Soft tissue sarcoma
Soft tissue sarcoma childhood
Spinal cord neoplasm
Squamous cell carcinoma
Squamous cell carcinoma of the head and neck
Status epilepticus
Stomach cancer, childhood
Stomach carcinoma
Superficial spreading melanoma
T-cell lymphoma 1A
Testicular cancer
Thyroid cancer, anaplastic
Thyroid cancer, follicular
Thyroid cancer, medullary
Tièche-Jadassohn nevus
Torsion dystonia
Transverse myelitis
Trypanosomiasis, Human West-African
Tuberculosis
Tuberous sclerosis
Tuberous sclerosis, type 1
Tuberous sclerosis, type 2
Turner syndrome
Tyrosinemia type 1
Urea cycle disorders
Uterine sarcoma
Ventricular fibrillation, idiopathic
Vernal keratoconjunctivitis
VIPoma
Von Willebrand disease
Wilson disease
Zollinger-Ellison syndrome

Appendix B: Selected orphan drug timeline

Year	Event
1964	Committee of the Public Health Service examines the effect of 1962 changes to FDA drug approval requirements on the commercial availability of un-patentable drugs and drugs for rare diseases.
1970s	Informal coalition of organizations focused on rare conditions promotes need for action to encourage development of drugs for these conditions.
1975	Interagency federal government committee publishes an interim report that describes problems related to drugs of limited commercial value and recommends further study.
1977	Congress creates Commission for the Control of Huntington's Disease and its Consequences, which called for more basic neurological research and product development for rare diseases.
1979	Interagency Task Force on Drugs of Limited Commercial Value (created in 1978) issues its final report.
1980-82	Congress holds hearings to learn more about problems of drugs for rare diseases.
1983	President signs Orphan Drug Act (P.L. 97-414), which creates a range of incentives for pharmaceutical manufacturers to develop drugs for rare diseases.
	National Organization for Rare Disorders, a federation of voluntary health organizations, is established by patients and families who worked together to get the Orphan Drug Act passed.
	FDA approves first two orphan drugs.
1984	Congress amends Orphan Drug Act ("Health Promotion and Disease Prevention Amendments" P.L. 98-551) to define a rare disease or condition as one that (1) affects fewer than 200,000 persons in the United States or (2) affects "more than 200,000 persons in the United States, but for which there is no reasonable expectation that the sales of the drug treatment will recover the costs."
	Congress directs the creation of a National Commission on Orphan Diseases to assess the research activities of NIH and other public and private organizations in connection with drug development.
1989	National Commission on Orphan Diseases issues report.
1990	Congress passes legislation to differentiate incentives for orphan drug development depending on commercial value, but the President vetoes it. Congress passes Safe Medical Devices Act of 1990 (P.L. 101-629), which (among other provisions) establishes the basis for the Humanitarian Device Exemption for devices to treat or diagnose a disease or condition that affects fewer than 4,000 individuals and that meet certain other conditions.
1992	Congress waives the payment of certain fees for drug and biologic product review for the sponsors of orphan drugs.
1993	The Office of Rare Diseases is established within the Office of the NIH Director.
1997	Congress permanently extends a tax credit of up to 50 percent for clinical research performed for designated orphan drugs (P.L. 105-34) and grants an exemption for orphan drugs from the usual drug approval application fees charged by the Food and Drug Administration (P.L. 105-115).
2002	Rare Diseases Act (P.L. 107-280) and Rare Disease Orphan Product Development Act (P.L. 107-281) are signed into law. The former legislatively establishes the NIH Office of Rare Diseases (now the Office of Rare Diseases Research) and requires NIH to support regional centers of excellence for clinical research into, training in, and

	demonstration of diagnostic, prevention, control, and treatment methods for rare diseases.
2003	NIH Office of Rare Diseases creates Rare Diseases Clinical Research Network, beginning with seven research consortia.
2007	FDA Amendments Act (P.L. 110-85) includes the Pediatric Medical Device Safety and Improvement Act, which provides incentives for industry and researchers to design devices for children.
2008	Congress enacts the Genetic Nondiscrimination Act (P.L. 110-233) to prohibit discrimination in health insurance and employment based on genetic information.
2009	NIH announces Therapeutics for Rare and Neglected Diseases Program and announces expansion of Rare Diseases Clinical Research Network.

Source: Rare diseases and orphan products: accelerating research and development, Institute of Medicine of the National Academies report, 2010; EY analysis.

Appendix C: Search methodology

This report used Medical Subject Headings (MeSH)-based searches to complete a comprehensive review of relevant literature. MeSH is an index of the biomedical literature that is used to provide consistent and uniform cataloging. MeSH terms describe the content of journal articles and eliminate the use of variant terms for the same concept. For example, articles pertaining to orphan drug manufacturing are categorized as "Orphan Drug Production."

The MeSH index is organized into tree structures with 16 main headings. For example, articles about strep throat will be categorized under "Streptococcus," and the tree structure is organized as: Organisms > Bacteria > Gram-Positive Bacteria > Gram-Positive Cocci > Streptococcaceae > Streptoccocus.[66] This structure allows searches of a broad term (Ear) to include the results of narrower terms as well (Ear, External; Ear, Middle; and Ear, Inner, as well as all narrower terms under each of these). Selected examples of searches used in this report are listed below:

- "Orphan Drug Production/statistics and numerical data"[MeSh] OR "Orphan Drug Production/economics"[MeSh]
- ("orphan drug production"[MeSH Terms] OR ("orphan"[All Fields] AND "drug"[All Fields] AND "production"[All Fields]) OR "orphan drug production"[All Fields] OR ("orphan"[All Fields] AND "drug"[All Fields]) OR "orphan drug"[All Fields]) AND (credit[All Fields] OR tax[All Fields])

The MeSH search methodology enables literature searches to be sensitive and specific. Specific search terms decrease the likelihood of missing important information and prevent the need to go through irrelevant articles, which can increase search efficiency.[67] More detailed searches increase precision, while the uniform indexing of articles removes the need to conduct searches using alternative spellings or small differences in terminology (e.g., manufacturing versus production).

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